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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/869,629	09/21/2001	Peter Knox	PA-9848	5709

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IP DEPARTMENT
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EXAMINER	
LAM, ANN Y	
ART UNIT	**PAPER NUMBER**
1641	

DATE MAILED: 12/02/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/869,629	KNOX ET AL.	
	Examiner	Art Unit	
	Ann Y. Lam	1641	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *12 September 2005*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-6,8-15,20,24-27,30 and 31* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-6,8-15,20,24-27,30 and 31* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Continued Examination Under 37 CFR 1.114

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on September 12, 2005 has been entered.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

1. Claim 30 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

The term "high" in claim 30 is a relative term which renders the claim indefinite. The term "high" is not defined by the claim, the specification does not provide a

standard for ascertaining the requisite degree, and one of ordinary skill in the art would not be reasonably apprised of the scope of the invention.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

2. Claims 1-6, 8-15, 20, 27 and 30 are rejected under 35 U.S.C. 103(a) as being unpatentable over Yu, 6,103,492, in view of Hall, et al., "Polarization-Enhanced NMR Spectroscopy of Biomolecules in Frozen Solution", Science, Vol. 276, May 1997.

Yu discloses performing an assay on a biological species using an assay reagent (col. 40, lines 37-38) containing at least one NMR active nucleus (col. 40, lines 40-45) to perform an assay, said assay reagent being introduced as an initial reagent, formed in situ during the assay or formed as a product of the assay (col. 8, lines 56-59);

and analyzing the assay reagent and/or the assay by NMR for a physical or chemical change in the biological species that is independent of the interaction of the biological species with the NMR active nucleus, ^{13}C or ^{15}N (i.e., binding between receptor and agent, column 9, lines 8-19; column 40, lines 37-45, and column 41, lines 41-48.)

Examiner notes that the step of "optionally using the NMR data obtained to generate further assay results" in subsection (d) of claim 1 is only an option and thus is not a required limitation in the claims.

Although Yu teaches use of NMR spectroscopy in conjunction with an NMR active nucleus to analyze an assay, Yu does not teach hyperpolarization of the NMR active nucleus by dynamic nuclear polarization. However, Hall et al. teach this limitation however.

Hall et al. teach use of dynamic nuclear polarization to hyperpolarize NMR active nucleus, ^{13}C and ^{15}N, (see page 930, especially second, third, and fifth paragraphs.) Hall et al. teach that the hyperpolarization enhances NMR spectroscopy of biomolecules.

It would have been obvious to one of ordinary skill in the art at the time the invention was made to hyperpolarize the NMR active nucleus in the Yu invention as taught by Hall et al. because Hall et al. teach that hyperpolarization of an NMR active nucleus provides the advantage of enhancing NMR detection.

As to the following claims, Yu teaches the limitations as follows.

As to claims 2 and 3, the NMR active nucleus is ^{13}C or ^{15}N (col. 40, line 45.)

As to claims 4 and 5, the assay reagent is a compound which contains an artificially high concentration of an NMR active nucleus, (i.e., the NMR active nucleus added as a label to a reagent is considered to be artificially high concentration; col. 8, lines 57-58, and col. 40, lines 40-45.) As to claim 5, since the limitation "in 1-10 defined

positions" is vague and indefinite (see above), the concentration of the NMR active nucleus in the Yu disclosure is considered to be in the 1-10 defined positions.

As to claim 6, the assay reagent is an organic compound comprising one or more NMR active nuclei associated with a bond which is broken during the course of the assay (i.e., the competitive displacement assay in col. 55, lines 54-56.)

As to claim 8, the analyzing step is repeated to generate information about a change with time of the assay reagent (i.e., a before and after detection.)

As to claim 9, the assay reagent is a nucleotide, or nucleotide analogue, polynucleotide, amino acid analogue, polypeptide or protein (col. 8 lines 45-59.)

As to claim 10, the assay is a nucleic acid hybridization assay, see column 8, lines 60-67.

As to claim 11, the assay is a binding assay, (column 8, lines 45-59, or column 9, lines 8-19.)

As to claim 12, the assay reagent is a compound labeled with at least one NMR active nucleus (col. 40, lines 37-45.)

As to claim 13, the assay is a binding study using micro-organisms or cultured cells, (column 38, lines 9-12.)

As to claim 27, Yu also teaches that the analyzing step is performed in an aerosol or flow-through device applied to aerosol droplets where the container is used to contain the assay reagent (col. 42, lines 11-20).

As to claims 14 and 15, Yu does not teach that the hyperpolarization transfer is repeated to enhance the signal-to-noise ratio (see claim 14); the shortening effect as

expressed by the improvement of signal-to-noise per unit time is a factor of 10 or more compared to known assay techniques without hyperpolarization (see claim 15). However, it would have been obvious to repeat the analysis steps, and to perform the NMR analysis step in the same container as the hyperpolarization transfer is carried out, since it is generally recognized that repeating known steps to obtain further data, or to perform NMR analysis step in the same container as the hyperpolarization transfer is carried out involves ordinary skill.

As to claim 20, Yu does not teach that the hyperpolarization transfer is carried out at a temperature of 4.2 K or less in the presence of a magnetic field of at least 1T. However, it has been held that where the general conditions of a claim are disclosed in the prior art, discovering the optimum or workable ranges involves only routine skill in the art (In re Aller, 105 USPQ 233), and in this case, the temperature as claimed by Applicant is an optimum or workable range.

As to claim 30, the assay reagent is considerd to contain an artificially high concentration of the NMR active nucleus

3. Claims 24 and 25 are rejected under 35 U.S.C. 103(a) as being unpatentable over Yu, 6,103,492, in view of Hall et al., "Polarization-Enhanced NMR Spectroscopy of Biomolecules in Frozen Solution", Science, Vol. 276, May 1997, as applied to claim 1, and further in view of Obremski, 6,110,749.

Yu in view of Hall et al disclose the invention substantially as claimed (see above with respect to claim 1), except for more than one assay being multiplexed (claim 24), and for the assay being performed in a multispot assay array (claim 25).

Obremski discloses a biological assay, wherein the assay is multiplexed and performed in a multispot assay array (col. 2, lines 66-67; col. 9, lines 19-20, and 32-33.)

It would have been obvious to one of ordinary skill in the art to provide a multiplexed or multispot assay as taught by Obremski using the Yu in view of Hall et al. method of analysis, as would be desirable for simultaneous assays as taught by Obremski, such simultaneous assays providing the advantage of allowing more assays to be performed quickly.

4. Claim 26 is rejected under 35 U.S.C. 103(a) as being unpatentable over Yu, 6,103,492, in view of Hall et al., "Polarization-Enhanced NMR Spectroscopy of Biomolecules in Frozen Solution", Science, Vol. 276, May 1997, as applied to claim 1, and further in view of Pines et al., 6,426,058

Also, as to claim 26, Yu in view of Hall et al. teach the invention substantially as claimed (see above), except for the analyzing step being performed by using both NMR spectroscopy and magnetic resonance imaging, and repeating the examination at least once.

Pines does however teach that a sample can be analyzed using both NMR spectroscopy and magnetic resonance imaging (see column 8, lines 60-63), and that

multiple parameters can be detected, and multiple techniques can be employed to collect and manipulate nuclear magnetic resonance data (col. 19, lines 3-5.)

It would have been obvious to one of ordinary skill in the art at the time the invention was made to utilize MRI detection as taught by Pines because Pines teaches that NMR spectroscopy and MRI detection can both be used to analyze a sample.

5. Claim 31 is rejected under 35 U.S.C. 103(a) as being unpatentable over Yu, 6,103,492, in view of Hall et al., "Polarization-Enhanced NMR Spectroscopy of Biomolecules in Frozen Solution", Science, Vol. 276, May 1997, as applied to claim 1, and further in view of Neild et al., "Uroscopy in the 21st Century: high-filed NMR spectroscopy", Nephrol Dial Transplant (1997), 12: 404-417.

Yu in view of Hall et al. teach the invention substantially as claimed (see above), except for the assay reagent being an organic compound comprising two or more NMR active nuclei associated with a chemical bond which is broken during the course of the assay such that when the bond is intact, the NMR active nuclei are spin coupled and when the bond is broken the spin coupling is disrupted. Neild et al. teach this limitation however.

Neild et al. teach that individual magnetic nuclei can interact with each other to produce additional splittings of the NMR peaks, called spin-spin or J coupling (see page 405, left column). Neild et al. teach that these interactions are also used for structural identification since they depend on molecular shapes and conformations (page 405, left

column.) It would have been obvious to one of ordinary skill in the art at the time the invention was made to utilize the spin coupling as taught by Neild et al. in the Yu invention because Neild teaches that such spin coupling provides the advantage of structural identification.

Response to Arguments

Applicant's arguments filed September 12, 2005 have been fully considered but are moot in view of the new grounds of rejections. Examiner notes however that in response to Applicant argument on pages 6-7 that Pines et al. (used in the previous Office action) requires hyperpolarized noble gas and that the presently amended claims cannot be obvious in light of Pines et al. because it does not involve the use of hyperpolarized gas, this argument is not persuasive because Applicant's presently amended claims do not preclude the use of hyperpolarized gas. In any case, new grounds of rejections are set forth in this Office action to reject Applicant's claims as they are intended to be interpreted by Applicant--that is, hyperpolarization of noble gases is not used by Hall et al.

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Ann Y. Lam whose telephone number is 571-272-0822. The examiner can normally be reached on M-Sat 11-6:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Long Le can be reached on 571-272-0823. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

A.L.

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11/28/05